POINTS TO CONSIDER

SCIENTIFIC ABSTRACT

Viral infection is one of the major causes of morbidity and mortality in patients who receive bone marrow transplantation (BMT) from unrelated or mismatched donors. This increased risk of infection relates to a number of factors including the immunosuppressive regimens these patients receive, delayed immune recovery and the greater genetic disparity between donor and recipient that result in defective interactions between antigen presenting cells and immune system effector cells. In most cases viral infection post BMT results from reactivation of latent virus and CMV, EBV and adenoviruses (Ad) are the commonest viral pathogens causing disease after transplant.

The incidence of Ad infection is >25% for patients at risk in the first 100 days after transplant [1] [2]. In the transplant population, adenovirus is recoverable from many sites and may cause hemorrhagic cystitis, pneumonitis, nephritis, hepatitis, colitis and pancreatitis, often with severe morbidity and mortality approaching 60%[3]. The most frequently used drug for the treatment of adenoviral infections is Cidofovir. But while there are occasional reports of responses to Cidofovir, no approved antiviral agent has proven efficacy for the treatment of severe Ad disease, nor are there any prospective randomized, controlled trials of potentially useful anti-Ad therapies [4]. With the increasing use of so-called submyeloablative or reduced intensity, highly immunosuppressive conditioning regimens, higher rates of Ad infections/reactivation have been observed due to prolonged immune suppression. The onset of Ad disease/reactivation has recently been reported to occur at a median of 18 days post-transplant (range –7/>+100) [2].

As viral complications in these patients are clearly associated with the lack of recovery of virus-specific cellular immune responses, reconstitution of the host with *in vitro* expanded CTLs is an effective approach to prevent and treat these diseases. Adoptive immunotherapy with *in vitro* expanded CTLs has proved effective in preventing and treating diseases related to Epstein Barr virus (EBV) infections [5; 6] and cytomegalovirus (CMV) reactivations[7] in hematopoietic stem cell transplant (HSCT) recipients. A promising strategy to generate donor-derived Ad-specific CTL is the infection of monocytes that direct the CTL response to viral capsid antigens[8]. This approach allows exposure to all proteins in the Ad protein coat, leading to presentation of multiple, undefined antigen epitopes. Hence, we now plan to use a recombinant Ad vector for infection of donor-derived monocytes. These infected monocytes will then be used as antigen presenting cells (APC) to generate Ad-specific CTL in vitro. For the expansion of the Ad-specific CTL, the second stimulation will use irradiated, Ad-infected monocytes and subsequent stimulations will use donor-derived Lymphoblastoid Cell Lines (LCL) transduced with the Ad vector as an APC [9].

We propose to evaluate this approach for the prophylaxis of Ad reactivation and disease in the recipients of matched unrelated donor or mismatched family member bone marrow allografts, who are at high risk for this complication. Initially, we will give the donor-derived Ad-specific CTLs to patients in a dose escalation study to determine their safety and immunologic and virologic efficacy.